Extension of the EM-algorithm using PLS to fit linear mixed effects models for high dimensional repeated data

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I. Introduction

To deal with repeated data

- Linear mixed effects models are highly recommended.
- A classical parameter estimation method: Expectation- Maximization (EM) algorithm.

To deal with high-dimensional data

- Reduction dimension methods can be used to summarize the numerous predictors in form of a small number of new components.
- Classical approach : Principal Component Regression (PCR)

$\hookrightarrow$ Does not consider the link between the outcome and the independent variables.

- Alternative method: Partial Least Squares (PLS)

$\hookrightarrow$ Takes the link between the outcome and the independent variables into account.

To solve the high dimensional issue in the repeated data context

$\hookrightarrow$ Introduction of a PLS step into the EM-algorithm for linear mixed models to reduce the high-dimensional data.

- **Idea:** At each iteration, the outcome data is substituted in the input of PLS by a pseudo-variable response whose expected value has a linear relationship with the covariates.

II. The linear mixed effects model

Definition of the linear mixed effects model

- $Y = (Y_1', \dots, Y_I')'$ with $Y_i = (Y_{i1}, \dots, Y_{in_i})'$ the vector of all measurements for the ith individual, $i = 1, \dots, I$.
- The linear mixed model for the response Y is defined as

$$Y = X\beta + U\xi + \varepsilon$$

with X the $n \times p$ design matrix associated to the p-vector fixed effects β, U the $n \times I$ design vector associated to the random effects $\xi = (\xi_1, \dots, \xi_I)'$, $\xi \sim \mathcal{N}(0_I, \tau^2 Id_I)$ and $\varepsilon \sim \mathcal{N}(0_n, \sigma^2 Id_n)$.

- The marginal distribution of the response Y is given by

$$Y \sim \mathcal{N}(X\beta, \Gamma) \qquad \text{with} \qquad \Gamma = \tau^2 UU' + \sigma^2 Id_n$$

The ML estimation approach using the EM-algorithm

- The log-likelihood associated with the complete data (y, ξ) is given by

$$L(\theta|y,\xi) = -\frac{1}{2}\Big\{(n+I)\ln 2\pi + I\ln\tau^2 + n\ln\sigma^2 + \frac{(y - X\beta - U\xi)'(y - X\beta - U\xi)}{\tau^2} + \frac{\xi^2}{\sigma^2}\Big\}$$

- At iteration $[t+1]$, the E-step consists of computing the expectation of the complete data log-likelihood given the observed data and a current value of the parameters $\theta^{[t]} = (\beta^{[t]}, \tau^{2[t]}, \sigma^{2[t]})$:

$$Q(\theta|\theta^{[t]}) = E\Big[L(\theta|y,\xi)|y, \theta^{[t]}\Big]$$

- The M-step consists of maximizing $Q(\theta|\theta^{[t]})$. It leads to the following explicit expressions:

$$\beta^{[t+1]} = \big(X'X\big)^{-1} X'\Big\{X\beta^{[t]} + \sigma^{2[t]}\,\Gamma^{[t]-1}(y - X\beta^{[t]})\Big\} \tag{1}$$

$$\tau^{2[t+1]} = \frac{1}{I}\Big\{\tau^{4[t]}(y - X\beta^{[t]})'\,\Gamma^{[t]-1}UU'\,\Gamma^{[t]-1}(y - X\beta^{[t]}) + \tau^{2[t]} - \tau^{4[t]}\mathbf{tr}(\Gamma^{[t]-1}UU')\Big\} \tag{2}$$

$$\sigma^{2[t+1]} = \frac{1}{n}\Big\{\sigma^{4[t]}(y - X\beta^{[t]})'\,\Gamma^{[t]-1}\,\Gamma^{[t]-1}(y - X\beta^{[t]}) + n\,\sigma^{2[t]} - \tau^{4[t]}\mathbf{tr}(\Gamma^{[t]-1})\Big\} \tag{3}$$

III. Extension of the EM-algorithm for high dimensional repeated data

Extension of the EM-algorithm using PLS (EM-PLS)

At iteration $[t+1]$:

- E-step: Compute the expectation of the complete data log-likelihood given the observed data and a current value of the parameters $\theta^{[t]}$
- M-step:
  - Define the pseudo-response variable $z^{[t+1]} = X\beta^{[t]} + \sigma^{2[t]}\,\Gamma^{[t]-1}(y - X\beta^{[t]})$
  - Perform PLS regression of the pseudo-response variable $z^{[t+1]}$ onto X:

$$\beta^{[t+1]} \leftarrow PLS(z^{[t+1]}, X, \kappa)$$

where κ is the PLS component number obtained by cross-validation.

  - Calculate new parameter values $\tau^{2[t+1]}$ and $\sigma^{2[t+1]}$ from Equations (2) and (3).

Extension of the EM-algorithm using PCR (EM-PCR)

Similarly, a PCR step is introduced into the EM-algorithm to reduce the high-dimensional data to low-dimensional features.

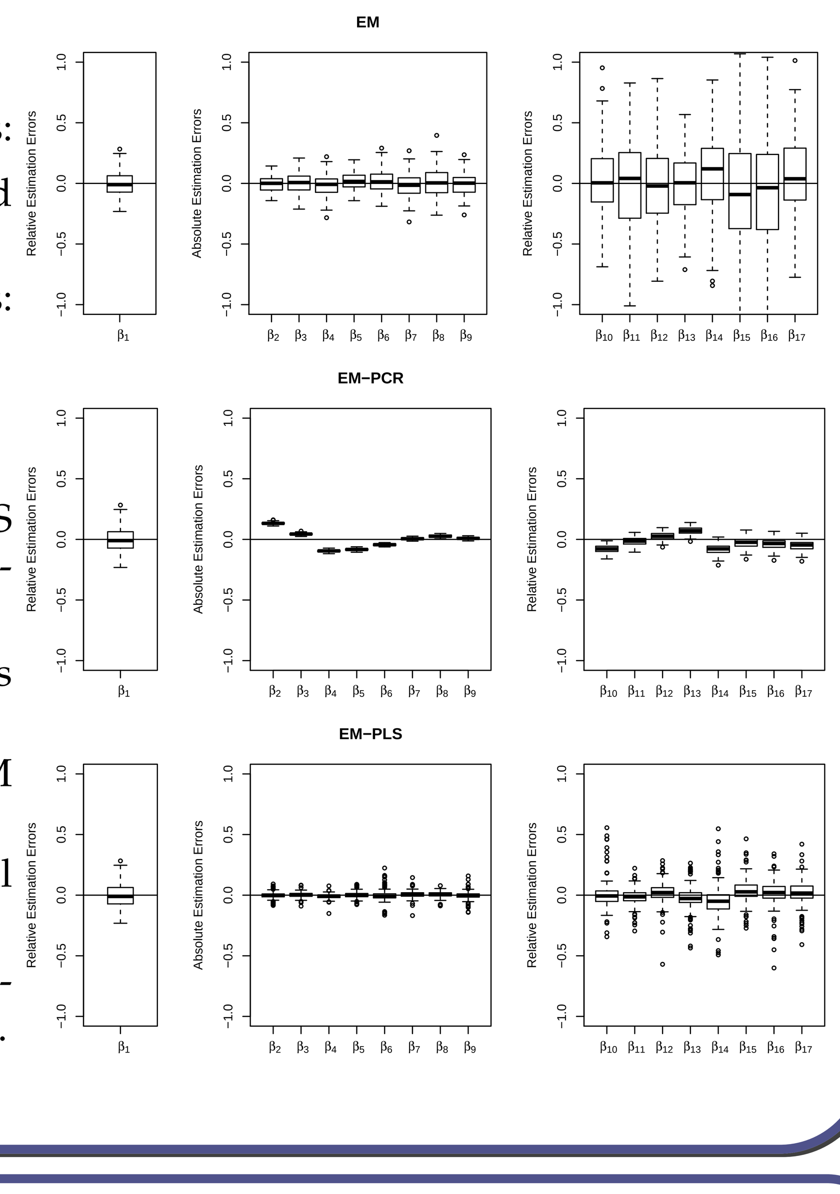
IV. A simulation study

Simulation framework

- For each individual i ($i = 1, \dots, 20$), $Y_i = X_i\beta + U_i\xi_i + \varepsilon_i$
- $X_i = (\mathbb{1}_{n_i}, X_i^1, X_i^2, X_i^3, X_i^4)$ where X_i^k is the $n_i \times 4$ fixed centered design matrix, $k = 1, \dots, 4$ and $U_i = \mathbb{1}_{n_i}$ with $n_i = 12 \quad \forall i = 1, \dots, 20$.
- $\beta = \{2.5, \{0\}^4, \{0\}^4, \{0.5\}^4, \{0.5\}^4\}$
- $\xi_i \sim \mathcal{N}(0, \tau^2)$ and $\varepsilon_i \sim \mathcal{N}(0_{12}, \sigma^2 Id_{12})$ where σ^2 and τ^2 are respectively defined from a given signal-to-noise ratio SNR and a given variances ratio TAU by

$\sigma^2 = \frac{1}{SNR^2}\frac{||X\beta - E(X\beta)||_2}{n}$ and $\tau^2 = \frac{\sigma^2}{TAU}$.

- $N = 100$ simulated data sets of size $n = 20 \times 12 = 240$ with different SNR and TAU values (learning set= 100 and test set=100).
- Criteria comparison:
  - Relative parameter estimation errors: $\frac{(\hat\beta_{jk} - \beta_j)}{\beta_j}$, $k = 1, \dots, 100$, $j = 1$ and $10, \dots, 17$
  - Absolute parameter estimation errors: $\hat\beta_{jk} - \beta_j$, $k = 1, \dots, 100$, $j = 2, \dots, 9$



Results for $SNR = 3$ and $TAU = 1$

$\hookrightarrow$ Concerning the β_j's estimation, EM-PLS method performs better than EM and EM-PCR methods:

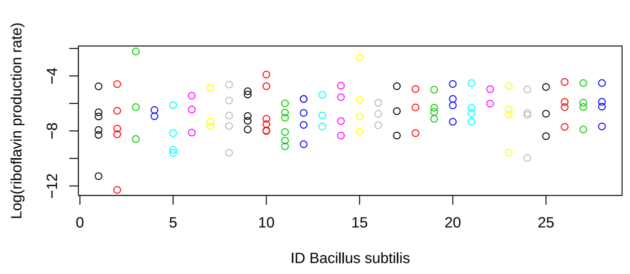
- On average, good parameter estimations are obtained with EM-PLS method
- Large variability is obtained with EM method for all β_j different to 0
- EM-PCR method performs poorly for all β_j equal to 0

$\hookrightarrow$ Globally, good estimation results are obtained with the three methods for τ^2 and σ^2.

V. An application: the Riboflavin data set

- Data about riboflavin (vitamin B2) production in Bacillus subtilis.
  - Response variable : logarithm of the riboflavin production rate
  - Design matrix : the logarithm of the expressions levels of 4088 genes (normalized)
- 28 Bacillus subtilis with a total number of samples equal to 111
  - Observations at different times in the same conditions
  - From 2 to 6 measurements by Bacillus subtilis

Logarithm of the riboflavin production rate (vitamin B2) produced in 28 Bacillus subtilis. Different colors are used for the different Bacillus subtilis.

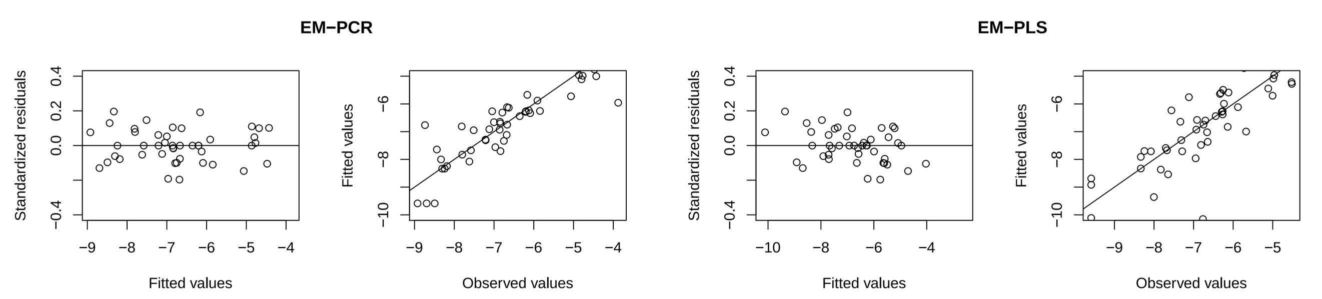


Method

- Subdivision of the data set into a learning set and a test set (ratio: 70 % - 30 %)
- Application of EM, EM-PCR and EM-PLS methods
- Computation of the mean absolute prediction error: $MAE = \frac{1}{n}\sum_{i=1}^n |\hat{y}_i - y_i|$
- Diagnostics plots: Normalized residuals vs fitted values and fitted values vs observed values plots.

Results

	EM-PCR	EM-PLS
Number of optimal components	8	8
MAE	0.43	0.63
$\hat\sigma^2$	0.62	0.02
$\hat\tau^2$	44.53	47.83



- No results with EM method because of numerical problems.
- Similar results are obtained with EM-PLS and EM-PCR methods.

$\hookrightarrow$ Possible improvement: a pre-selection step such as a Sure Independence Screening (SIS) procedure could be applied.

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